DEP $ RSR

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Fabienne Andrea FULDE, et al
Serial No.: 10/517,497 Group No.:
Filed: December 10, 2004 Examiner.:
For: IN VITRO SCREENING OF CELLULAR EVENTS USING 3D CELL CULTURE SYSTEM

Attorney Docket No.: U 015529-5

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR REFUND

Deposit Account 12-0425 was charged $1050.00 for extra total claims over twenty (Fee Code 1615); $800.00 for extra independent claims (Fee Code 1614) and $360.00 for multiple dependent claims (Fee Code 1616) on April 14, 2005 (Control Nos. 2, 3 & 4).

CERTIFICATION UNDER 37 C.F.R. 1.8(a) and 1.10*
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I hereby certify that, on the date shown below, this correspondence is being:

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37 C.F.R. 1.8(a)

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Date: July 28, 2005

Signature

CLIFFORD J. MASS
(type or print name of person certifying)

Adjustment date: 11/10/2005 RWHITE1
08/12/2005 PKIDWELL 00000002 120425 10517497
FC:1615 1050.00 CR

Adjustment date: 11/10/2005 RWHITE1
08/12/2005 PKIDWELL 00000002 120425 10517497
01 FC:1614 800.00 CR

Adjustment date: 11/10/2005 RWHITE1
08/12/2005 PKIDWELL 00000002 120425
02 FC:1616 360.00 CR

*WARNING: *Each paper or fee filed by "Express Mail" must have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. 1.10(b). "Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will not be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.*

However, no claim fee charge was authorized and according to 37 CFR 1.492(g), if additional fees are required they only must be paid prior to the expiration of the term period set for reply by the Office in any Notice of Fee deficiency, which has not issued.

In the meantime, a Preliminary Amendment with stamped postcard cancelling the multiple dependent claims (copy attached) and payment of $1600.00 by check no. 053374 for sixteen (16) extra total claims and four (4) extra independent claims was filed on June 16, 2005.

Therefore, refund of the total charges of $2210.00 by credit to Deposit Account 12-0425 is requested.

Respectfully submitted,

CLIFFORD J. MASS
LADAS & PARRY LLP
26 WEST 61ST STREET
NEW YORK, NEW YORK 10023
REG. NO.30,086(212)708-1890

Practitioner's Docket U 015529-5 *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Fabienne Andrea FULDE, et al

Serial No.: 10/517,497 Group No.:

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P. O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT TRANSMITTAL

WARNING: *Failure to file a complete response in compliance with § 1.135(c) leads to a reduction in patent term adjustment - See § 1.704(c)(7).*

1. Transmitted herewith is an amendment for this application.

STATUS

2. The application is qualified as
   - ☐ a small entity.
   - ☒ other than a small entity.

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37 C.F.R. 1.8(a)

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37 C.F.R. 1.10*

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TRANSMISSION

☐ transmitted by facsimile to the Patent and Trademark Office. to (703) 872-9306

Date: June 16, 2005

Signature

CLIFFORD J. MASS
(type or print name of person certifying)

* *Only the date of filing (§ 1.6) will be the date used in a patent term adjustment calculation, although the date on any certificate of mailing or transmission under § 1.8 continues to be taken into account in determining timeliness. See § 1.703(f). Consider "Express Mail Post Office to Addressee" (§ 1.10) or facsimile transmission (§ 1.6(d)) for the reply to be accorded the earliest possible filing date for patent term adjustment calculations.*

EXTENSION OF TERM

NOTE: "Extension of Time in Patent Cases (Supplement Amendments) — If a timely and complete response has been filed after a Non-Final Office Action, an extension of time is not required to permit filing and/or entry of an additional amendment after expiration of the shortened statutory period.

If a timely response has been filed after a Final Office Action, an extension of time is required to permit filing and/or entry of a Notice of Appeal or filing and/or entry of an additional amendment after expiration of the shortened statutory period unless the timely-filed response placed the application in condition for allowance. Of course, if a Notice of Appeal has been filed within the shortened statutory period, the period has ceased to run." Notice of December 10, 1985 (1061 O.G. 34-35).

NOTE: See 37 C.F.R. §1.645 for extensions of time in interference proceedings, and 37 C.F.R. § 1.550(c) for extensions of time in reexamination proceedings.

NOTE: 37 C.F.R. § 1.704(b)". . . an applicant shall be deemed to have failed to engage in reasonable efforts to conclude processing or examination of an application for the cumulative total of any periods of time in excess of three months that are taken to reply to any notice or action by the Office making any rejection, objection, argument, or other request, measuring such three-month period from the date the notice or action was mailed or given to the applicant, in which case the period of adjustment set forth in § 1.703 shall be reduced by the number of days, if any, beginning on the day after the date that is three months after the date of mailing or transmission of the Office communication notifying the applicant of the rejection, objection, argument, or other request and ending on the date the reply was filed. The period, or shortened statutory period, for reply that is set in the Office action or notice has no effect on the three-month period set forth in this paragraph."

3. The proceedings herein are for a patent application and the provisions of 37 C.F.R. 1.136 apply.

(complete (a) or (b), as applicable)

(a) ☐ Applicant petitions for an extension of time under 37 C.F.R. 1.136 (fees: 37 C.F.R. 1.17(a)(1)-(4)) for the total number of months checked below:

	Extension (months)	Fee for other than small entity	Fee for small entity
☐	one month	$ 120.00	$ 60.00
☐	two months	$ 450.00	$ 225.00
☐	three months	$ 1,020.00	$ 510.00
☐	four months	$ 1,590.00	$ 795.00
☐	five months	$ 2,160.00	$ 1,080.00

Fee: $_____

If an additional extension of time is required, please consider this a petition therefor.

(check and complete the next item, if applicable)

☐ An extension for _____ months has already been secured. The fee paid therefor of $ _____ is deducted from the total fee due for the total months of extension now requested.

Extension fee due with this request $ _____

OR

(b) ☒ Applicant believes that no extension of term is required. However, this is a conditional petition being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition for extension of time.

FEE FOR CLAIMS

4. The fee for claims (37 C.F.R. 1.16(b)-(d)) has been calculated as shown below:

	(Col. 1)		(Col. 2)	(Col. 3)	SMALL ENTITY			OTHER THAN A SMALL ENTITY	
	Claims Remaining After Amendment		Highest No. Previously Paid For	Present Extra	Rate	Addit. Fee	*OR*	Rate	Addit. Fee
Total	*36	Minus	**20	= 16	x $ 25	$		x $ 50=	$800
Indep.	* 7	Minus	*** 3	= 4	x $ 100	$		x $ 200	$800
☐First Presentation of Multiple Dependent Claims					+ $180=	$		+ $360=	$
				Total Addit. Fee		$ ___	*OR*	Total Addit. Fee	$1600

* If the entry in Col. 1 is less than the entry in Col. 2, write "O" in Col. 3,

** If the "Highest No. Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest No. Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest No. Previously Paid For" (Total or Indep.) is the highest number found in the appropriate box in Col. 1 of a prior amendment or the number of claims originally filed.

WARNING: *"After final rejection or action (§ 1.113) amendments may be made canceling claims or complying with any requirement of form which has been made." 37 C.F.R. 1.116(a) (emphasis added).*

(complete (c) or (d), as applicable)

(c) ☐ No additional fee for claims is required.

OR

(d) ☒ Total additional fee for claims required $ 1600

FEE PAYMENT

5. ☒ Attached is a check in the sum of $ 1600

☐ Charge Account No. 12-0425 the sum of $ _____

A duplicate of this transmittal is attached.

FEE DEFICIENCY OR OVERPAYMENT

NOTE: If there is a fee deficiency and there is no authorization to charge an account, additional fees are necessary to cover the additional time consumed in making up the original deficiency. If the maximum, six-month period has expired before the deficiency is noted and corrected, the application is held abandoned. In those instances where authorization to charge is included, processing delays are encountered in returning the papers to the PTO Finance Branch in order to apply these charges prior to action on the cases. Authorization to charge the deposit account for any fee deficiency should be checked. See the Notice of April 7, 1986, (1065 O.G. 31-33).

6. ☒ If any additional extension and/or fee is required, charge Account No. 12-0425.

AND/OR

☒ If any additional fee for claims is required, charge Account No. 12-0425

AND/OR

☒ Refund any overpayment to Account No. 12-0425.

SIGNATURE OF PRACTITIONER

Reg. No. 30086

CLIFFORD J. MASS
(type or print name of practitioner)

Tel. No. 212-708-1890

P.O. Address

c/o Ladas & Parry LLP
26 West 61 Street
New York, N.Y. 10023

Customer No.:

00140

PATENT TRADEMARK OFFICE

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Fabienne Andrea FULDE, et al
Serial No.: 10/517,497 Group No.:
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Attorney Docket No.: U 015529-5

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Prior to an examination of this application, please amend the application as follows:

CERTIFICATION UNDER 37 C.F.R. 1.8(a) and 1.10*
(When using Express Mail, the Express Mail label number is mandatory; Express Mail certification is optional.)

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37 C.F.R. 1.8(a)

☒ with sufficient postage as first class mail.

37 C.F.R. 1.10*

☐ as "Express Mail Post Office to Address" Mailing Label No. _____ **(mandatory)**

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☐ transmitted by facsimile to the Patent and Trademark Office. to **(708) 872-9306**

Date: June 16, 2005

Signature

CLIFFORD J. MASS
(type or print name of person certifying)

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IN THE SPECIFICATION:

Page 1, before the first line, insert the following paragraph:

--This application claims the benefit of U.S. Provisional Application number 60/388,483, filed June 13, 2002 and incorporates the same by reference.--

IN THE CLAIMS:

Claim 1 (original) A screening method for compounds having a modulating effect on cellular development and/or cell differentiation and/or cellular processes, said method comprising the following steps:

a) cultivating cells harboring a promoter-reporter construct in a 3D micro-culture under conditions mimicking the natural in vivo environment (3D tissue-like conditions) of said cells, or cultivating said cell in a 2D culture on bioinductive material,

b) contacting said cells with a test compound and comparing the read-out of the promoter-reporter construct to a control.

Claim 2 (original) The method of claim 1, wherein said 3D tissue-like conditions comprise either 3D aggregated cells, cultivated under high cellular density only, and/or cells cultivated with natural or synthetic scaffold/biomaterial.

Claim 3 (original) The method of claim 2, wherein said scaffolds/biomaterials are a biomaterial substrate or scaffold that promotes normal physiological activity, in particular scaffolds/biomaterials selected from the group of natural scaffolds/biomaterials consisting of alginate, agarose, hyaluronic acid, collagen, proteoglycan and mixtures thereof, or from the group of synthetic scaffolds/biomaterials consisting of Skelite™, polyHEMA, polyglycolic acid (PGA), polylactic acid (PLA) and mixtures of PGA and PLA.

Claim 4 (currently amended) The screening method of ~~anyone of claims~~ claim 1 ~~to 3~~, wherein said cells are derived from healthy or pathological musculoskeletal tissues or precursor cells being able to differentiate and form *de novo* musculoskeletal tissue, preferably said cells stem from humans.

Claim 5 (original) The method of claim 4, wherein said tissue is selected from the group consisting of chondrocytes, bone cells, rheumatoid cells, osteoarthritic chondrocytes, stem cells, mesenchymal cells, cartilage or bone tumor cells.

Claim 6 (currently amended) The screening method of ~~anyone of claims~~ claim 1 ~~to 5~~, wherein said promoter is selected from the group consisting of human COL1, COL2, SOX9, COMP, MMP2, and aggrecanase-1 (ADAMTS4).

Claim 7 (currently amended) The screening method of ~~anyone of claims~~ claim 1 ~~to 6~~, wherein said reporter is selected from the group of GFP, luciferase, β-galactosidase, chloramphenicol acetyltransferase gene (CAT).

Claim 8 (currently amended) The screening method of ~~anyone of claims~~ claim 1 ~~to 7~~, wherein said cells stem from humans and said promoter-reporter construct comprises a reporter gene under control of a human promoter wherein said promoter is selected from the group consisting of human COL1, human COL2, human SOX9, human COMP, human MMP2, and human aggrecanase-1 (ADAMTS4) and said reporter gene encodes a protein with an activity that can

be detected by colorimetric or fluorescent methods, in particular said reporter is selected from the group consisting of GFP, luciferase, β-galactosidase, chloramphenicol acetyltransferase gene (CAT).

Claim 9 (currently amended) The screening method of ~~anyone of claims~~ claim 1 ~~to 8~~, wherein said cells comprise more than one promoter-reporter construct.

Claim 10 (currently amended) The screening method of ~~anyone of claims~~ claim 1 ~~to 9~~, wherein said test compounds are selected from the group consisting of chemical libraries, natural product libraries, peptide libraries, cDNA libraries and combinatorial libraries.

Claim 11 (currently amended) The screening method of ~~anyone of claims~~ claim 1 ~~to 10~~, wherein said method is performed in a multiplate culture format e.g. 96 or 384-mulitwells.

Claim 12 (original) The screening method of claim 11, wherein the 3D micro cultures are produced in an automated fashion e.g. by robotic system.

Claim 13 (currently amended) The screening method of ~~anyone of claims~~ claim 1 ~~to 12~~, wherein said cells are contacted with an activator or suppressor of said promoter and with a test compound.

Claim 14 (currently amended) The screening method of ~~anyone of claims~~ claim 1 ~~to 13~~,

wherein said method is used as a quality control tool to assess the chondrogenic potential of isolated cells prior to implantation within cell-based therapies.

Claim 15 (currently amended) The screening method of ~~anyone of claims~~ claim 1 ~~to 13~~, wherein said method is used as a quality control tool to assess a process producing *in vitro* tissue-engineered cartilage constructs usable for treatment of cartilage defects.

Claim 16 (currently amended) The screening method of ~~anyone of claims~~ claim 1 ~~to 13~~, wherein said method is used as a tool to assess the cell potency and such the suitability of cells for cell therapy and/or tissue engineered therapy.

Claim 17 (original) ~~Use of~~ A method for producing a transgenic animal comprising transforming an animal with a promoter-reporter construct wherein said reporter is selected from the group consisting of GFP, luciferase, β-galactosidase, chloramphenicol acetyltransferase gene (CAT) and said promoter is selected from the group consisting of COL1, COL2, SOX9, COMP, MMP2, and aggrecanase-1 (ADAMTS4)~~, for the construction of transgenic animals, preferably transgenic mice~~.

Claim 18 (currently amended) A transgenic animal comprising a promoter-reporter construct, wherein said construct comprises a reporter selected ~~form~~ from the group consisting of GFP, luciferase, β-galactosidase, chloramphenicol acetyltransferase gene (CAT) and a promoter selected from the group consisting of COL1, COL2, SOX9, COMP, MMP2 and

aggrecanase-1 (ADAMTS4).

Claim 19 (original) A cell line derived from the transgenic animal of claim 18.

Claim 20 (currently amended) ~~Use of~~ A method comprising using the transgenic animal of claim 18 ~~or the cell line of claim 19~~ in a screening method for screening compounds having a modulating effect on cellular development and/or cell differentiation and/or cellular processes.

Claim 21 (original) A DNA construct for cell transfection comprising a reporter gene under control of a human promoter wherein said promoter is selected from the group consisting of human COL1, human COL2, human SOX9, human COMP, human MMP2, and human aggrecanase-1 (ADAMTS4) and said reporter gene encodes a protein with an activity that can be detected by colorimetric or fluorescent methods.

Claim 22 (original) The DNA construct of claim 21, wherein said reporter is selected from the group consisting of GFP, luciferase, β-galactosidase, chloramphenicol acetyltransferase gene (CAT).

Claim 23 (currently amended) A cell comprising a reporter construct of claim 21 ~~or 22~~.

Claim 24 (currently amended) A cell line comprising a reporter construct of claim 21 ~~or 22~~.

Claim 25 (currently amended) The cell or cell line of claim 23 ~~or 24~~, wherein said cells are derived from healthy or pathological musculoskeletal tissues or precursor cells being able to differentiate and form *de novo* musculoskeletal tissue, preferably said cells stem from humans.

Claim 26 (original) The cell or cell line of claim 25, wherein said cells are selected from the group consisting of chondrocytes, bone cells, rheumatoid cells, osteoarthritic chondrocytes, stem cells, mesenchymal cells, cartilage or bone tumor cells.

Claim 27 (currently amended) ~~Use of a cell of anyone of claims 23, 25 or 26 or~~ A method comprising performing a cellular screening assay with a cell line of ~~anyone of claims~~ claim 24 ~~to 26 in a cellular screening assay~~.

Claim 28 (currently amended) ~~Use of~~ A method comprising using a cell of ~~anyone of claims~~ claim 23, ~~25 or 26~~ for the *in vitro* formation of tissue~~, preferably cartilage tissue~~.

Claim 29 (original) A method for testing whether a material has bioinductive characteristics, said method comprising the following steps:

culturing cells harboring a promoter-reporter construct on the material to be tested and comparing the read-out of the promoter-reporter construct to a control.

Claim 30 (currently amended) The method of claim 29, wherein said cells are human cells~~; preferably cells as defined in claim 4 or 5~~.

Claim 31 (currently amended) The method of claim 29 ~~or 30~~, wherein said reporter is selected from the group consisting of GFP, luciferase, β-galactosidase, chloramphenicol acetyltransferase gene (CAT) ~~defined in claim 7~~ and the promoter is selected from the group consisting of human COL1, COL2, SOX9, COMP, MMP2, and aggrecanase-1 (ADAMTS4) ~~defined in claim 6~~.

Claim 32 (original) A method for testing whether a biomaterial is degraded or resorbed *in vivo* or *in vitro*, said method comprising the following steps:

culturing cells harboring a promoter-reporter construct on the material to be tested and monitoring expression of the reporter gene in said cells.

Claim 33 (currently amended) The method of claim 32, wherein said cells are human cells~~;~~ ~~preferably cells as defined in claim 4 or 5~~.

Claim 34 (currently amended) The method of claim 32 ~~or 33~~, wherein said reporter is selected from the group consisting of GFP, luciferase, β-galactosidase, chloramphenicol acetyltransferase gene (CAT) ~~defined in claim 7~~ and the promoter is selected from the group consisting of human COL1, COL2, SOX9, COMP, MMP2, and aggrecanase-1 (ADAMTS4) ~~defined in claim 6~~.

Claim 35 (original) A method for the quality control of cells cultivated *in vitro* comprising:

transfecting cells that have been cultured in vitro with a key marker promoter-reporter

construct.and cultivating said transfected cells in a 3D culture and

detection of the reporter read-out which is indicative for differentiated cells.

Claim 36 (currently amended) The method of claim 35, wherein said cells are selected from the group consisting of chondrocytes, bone cells, rheumatoid cells, osteoarthritic chondrocytes, stem cells, mesenchymal cells, cartilage or bone tumor cells ~~defined in claim 4 or 5~~, the promoter is selected from the group consisting of GFP, luciferase, β-galactosidase, chloramphenicol acetyltransferase gene (CAT) ~~defined in claim 7~~ and the promoter is selected from the group consisting of human COL1, COL2, SOX9, COMP, MMP2, and aggrecanase-1 (ADAMTS4) ~~defined in claim 6~~.

REMARKS

The above amendments are made to remove multiple dependencies and double dependencies form the claims and to rewrite "use" claims as method claims in accordance with the provisions of 35 USC 101.

Respectfully submitted,

CLIFFORD J. MASS
LADAS & PARRY LLP
26 WEST 61ST STREET
NEW YORK, NEW YORK 10023
REG. NO.30,086(212)708-1890

U 015529-5 June 16, 2005

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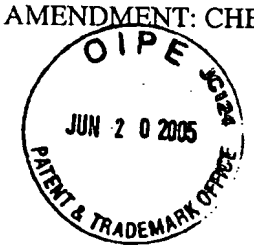
AMENDMENT TRANSMITTAL: PRELIMINARY AMENDMENT: CHECK NO. P 053374 IN THE AMOUNT OF $1600



Filed _____
CJM/bds